IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Douglas A. Heltzman et al.

Serial No.: 09/811,088

Filed: March 16, 2001

For: NOVEL GENES ENCODING PROTEINS HAVING PROGNOSTIC, DIAGNOSTIC, PREVENTIVE, THERAPEUTIC, AND OTHER USES

Attorney Docket No.: MPI2000-540OMNI(M)

Group Art Unit: 1645

Assistant Commissioner for Patents
Washington, DC 20231

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November 30, 2001
Date of Signature and of Mail Deposit

By: Mary MacKinnon
Mary MacKinnon

PRELIMINARY AMENDMENT

Prior to examination, please amend the above-identified application as follows:

In the Title:

Please replace the title with:

"NOVEL GENES ENCODING PROTEINS HAVING PROGNOSTIC, DIAGNOSTIC, PREVENTIVE, THERAPEUTIC AND OTHER USES"

In the Sequence Listing:

Please replace the title with:

"NOVEL GENES ENCODING PROTEINS HAVING PROGNOSTIC, DIAGNOSTIC, PREVENTIVE, THERAPEUTIC AND OTHER USES"

In the Specification:

Please amend the specification as follows. For the Examiner's convenience, a marked up version of paragraphs in the specification is enclosed (Exhibit A), in which text added to these claims is underlined and text deleted is struck through. A version of amended paragraphs in the specification as of the instant amendment is enclosed as well (Exhibit B).

On page 9, please amend the paragraph beginning on line 8 to read as follows:

Also considered within the scope of the invention is a nucleic acid molecule that: hybridizes under stringent conditions to cDNA sequence contained within ATCC Accession No. 98367; hybridizes under stringent conditions to cDNA sequence contained within ATCC Accession No. 98368; is 85% identical to SEQ ID NO:1B (Figures 3A-1 to 3C); is 85% identical to SEQ ID NO:3B (Figures 4A-1 to 4C); is 95% identical to SEQ ID NO:1B; is 95% identical to SEQ ID NO:3B; is 85% identical to cDNA sequence contained within ATCC Accession No. 98367; is 85% identical to cDNA sequence contained within ATCC Accession No. 98368; is 95% identical to cDNA sequence contained within ATCC Accession No. 98367; is 95% identical to cDNA sequence contained within ATCC Accession No. 98368; hybridizes under stringent conditions to nucleotides 128 to 1447 of SEQ ID NO:1B (Figures 3A-1 to 3C); or hybridizes under stringent conditions to nucleotides 128 to 1360 of SEQ ID NO:3B (Figures 4A-1 to 4C). Polypeptides encoded by these nucleic acids are also considered within the scope of the invention.

On page 10, please amend the paragraph beginning on line 24 to read as follows:

The invention also features substantially pure or isolated huchordin polypeptides, including those that correspond to various functional domains of huchordin, or fragments thereof. The polypeptides of the invention encompass amino acid sequences that are substantially identical to the amino acid sequence shown in Figures 6A-1 to 6C-2 (SEQ ID NO:2D).

On page 19, please amend the five paragraphs beginning on line 16 to read as follows:

Figures 3A-1 to 3C are a representation of the nucleic acid sequence of Tango-63d (SEQ ID NO:1B; open reading frame from nucleotide 128-1450) and the amino acid sequence of the polypeptide it encodes (SEQ ID NO:2B).

Figures 4A-1 to 4C are a representation of the nucleic acid sequence of Tango-63e (SEQ ID NO:3B; open reading frame from nucleotide 128-1363) and the amino acid sequence of the polypeptide it encodes (SEQ ID NO:4B).

Figures 5A-1 to 5B are a depiction of the nucleotide sequence encoding Tango-67 and 3' and 5' non-translated sequence (SEQ ID NO:1C; open reading from nucleotide 182-853) and the amino acid sequence (SEQ ID NO:2C) of Tango-67.

Figures 6A-1 to 6C-2 are a depiction of the sequence of a cDNA encoding huchordin (SEQ ID NO:1D; open reading from nucleotide 1-2604) and the deduced amino sequence (SEQ ID NO:2D) of huchordin.

Figures 7A-7C are an alignment of a portion of the amino acid sequence of huchordin (upper sequence of each pair) and a portion of amino acid sequence of *Xenopus* chordin (lower sequence of each pair; SEQ ID NO:4D).

On page 44, please amend the paragraph beginning on line 27 to read as follows:

Two different forms of Tango-63 have been identified in the prostate cDNA library through EST sequencing and screening of the lambda phage library for the isolation of additional clones (Tango-63d and Tango-63e). Tango-63d encodes a polypeptide of 440 amino acids (encoded by nucleotides 128 to 1447 of SEQ ID NO:1B and shown in Figures 3A-1 to 3C); and Tango-63e encodes a polypeptide of 411 amino acids (encoded by nucleotides 128 to 1360 of SEQ ID NO:3B and shown in Figures 4A-1 to 4C). The polypeptide encoded by Tango-63e is identical to that encoded by Tango-63d, with the exception of the deletion of amino acids 183-211 (encoded by nucleotides 677-760) in the Tango-63d sequence. The deleted amino acids are those just amino-terminal to the transmembrane domain in Tango-63d. Tango-63d and Tango-63e are novel polypeptides that represent new members of the tumor necrosis factor (TNF) receptor superfamily.

On page 51, please amend the two paragraphs beginning on line 8 to read as follows:

either the 5' or 3' non-translated, non-coding regions of the gene of the invention, e.g., the human gene shown in ~~FIG. 1, FIG. 3, FIG. 4, FIG. 5, or FIG. 6~~ Figure 1, Figures 3A-1 to 3C, Figures 4A-1 to 4C, Figures 5A-1 to 5B, or Figures 6A-1 to 6C-2, could be used in an antisense approach to inhibit translation of endogenous thymotaxin, Tango-63d, Tango-63e, Tango-67, or huchordin mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon.

In the Abstract:

Please replace the title with:

"NOVEL GENES ENCODING PROTEINS HAVING PROGNOSTIC, DIAGNOSTIC, PREVENTIVE, THERAPEUTIC AND OTHER USES"

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REMARKS

Applicants have changed the title of the present application to correctly speli "prognostic." Applicants have also changed *the names only* of the figures throughout the specification, to appropriately reflect the formalized figures submitted herewith. No new matter has been added, and Applicant submits that all of the claims are now in condition for allowance, which action is requested.

Date: 30 NOV 2001

Respectfully submitted,
MILLENNIUM PHARMACEUTICALS, INC.

By _____

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EXHIBIT A

MARKED UP VERSION OF PARAGRAPHS IN THE SPECIFICATION AS OF THE INSTANT AMENDMENT FILED NOVEMBER 30, 2001

In the Title:

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On page 10, please amend the paragraph beginning on line 24 to read as follows:

The invention also features substantially pure or isolated huchordin polypeptides, including those that correspond to various functional domains of huchordin, or fragments thereof. The polypeptides of the invention encompass amino acid sequences that are substantially identical to the amino acid sequence shown in ~~FIG. 6~~ Figures 6A-1 to 6C-2 (SEQ ID NO:2D).

On page 19, please amend the five paragraphs beginning on line 16 to read as follows:

~~Figure 3 is~~ Figures 3A-1 to 3C are a representation of the nucleic acid sequence of Tango-63d (SEQ ID NO:1B; open reading frame from nucleotide 128-1450) and the amino acid sequence of the polypeptide it encodes (SEQ ID NO:2B).

~~Figure 4 is~~ Figures 4A-1 to 4C are representation of the nucleic acid sequence of Tango-63e (SEQ ID NO:3B; open reading frame from nucleotide 128-1363) and the amino acid sequence of the polypeptide it encodes (SEQ ID NO:4B).

~~Figure 5 is~~ Figures 5A-1 to 5B are a depiction of the nucleotide sequence encoding Tango-67 and 3' and 5' non-translated sequence (SEQ ID NO:1C; open reading from nucleotide 182-853) and the amino acid sequence (SEQ ID NO:2C) of Tango-67.

~~Figure 6 is~~ Figures 6A-1 to 6C-2 are a depiction of the sequence of a cDNA encoding huchordin (SEQ ID NO:1D; open reading from nucleotide 1-2604) and the deduced amino sequence (SEQ ID NO:2D) of huchordin.

~~Figure 7 is~~ Figures 7A-7C are an alignment of a portion of the amino acid sequence of huchordin (upper sequence of each pair) and a portion of amino acid sequence of *Xenopus* chordin (lower sequence of each pair; SEQ ID NO:4D).

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Figures 4A-1 to 4C are a representation of the nucleic acid sequence of Tango-63e (SEQ ID NO:3B; open reading frame from nucleotide 128-1363) and the amino acid sequence of the polypeptide it encodes (SEQ ID NO:4B).

Figures 5A-1 to 5B are a depiction of the nucleotide sequence encoding Tango-67 and 3' and 5' non-translated sequence (SEQ ID NO:1C; open reading from nucleotide 182-853) and the amino acid sequence (SEQ ID NO:2C) of Tango-67.

Figures 6A-1 to 6C-2 are a depiction of the sequence of a cDNA encoding huchordin (SEQ ID NO:1D; open reading from nucleotide 1-2604) and the deduced amino sequence (SEQ ID NO:2D) of huchordin.

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SEQ ID NO:3B and shown in Figures 4A-1 to 4C). The polypeptide encoded by Tango-63e is identical to that encoded by Tango-63d, with the exception of the deletion of amino acids 183-211 (encoded by nucleotides 677-760) in the Tango-63d sequence. The deleted amino acids are those just amino-terminal to the transmembrane domain in Tango-63d. Tango-63d and Tango-63e are novel polypeptides that represent new members of the tumor necrosis factor (TNF) receptor superfamily.

On page 51, please amend the two paragraphs beginning on line 8 to read as follows:

A novel open reading frame was identified during genomic sequencing of a human bacterial artificial chromosome. The open reading frame was located approximately 4 kb upstream of the thrombopoietin gene. A genomic fragment within the open reading frame was used to probe a human brain cDNA library (Clontech; Palo Alto, CA). A near full-length cDNA clone, lacking only two nucleotides of the initial Met codon, was identified. The identity of the missing nucleotides was confirmed by comparison to the genomic sequence. The cDNA clone encoded a 867 amino acid protein. The cDNA sequence of huchordin is shown in Figures 6A-1 to 6C-2 (SEQ ID NO:1D). The huchordin encoding portion of this cDNA extends from nucleotide 1 to nucleotide 2601 (SEQ ID NO:3D). The amino acid sequence of huchordin is also shown in Figures 6A-1 to 6C-2 (SEQ ID NO:2D).

Huchordin is predicted to be a secreted protein having a signal sequence extending from amino acid 1 to amino acid 26. At the amino acid level, huchordin is 53% identical to *Xenopus* chordin (Sasai et al., *Cell* 79:779, 1994). Figures 7A to 7C are an alignment of a portion of the amino acid sequence of huchoridin and a portion of the amino acid sequence of *Xenopus* chordin (SEQ ID NO:4D). Variants of huchordin that are more likely to retain activity do not have alterations at the amino acid positions conserved between huchordin and chordin.

On page 75, please amend the paragraph beginning on line 11 to read as follows:

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs recently have been shown to be effective at inhibiting translation of

mRNAs as well (Wagner, *Nature* 372:333, 1984). Thus, oligonucleotides complementary to either the 5' or 3' non-translated, non-coding regions of the gene of the invention, e.g., the human gene shown in Figure 1, Figures 3A-1 to 3C, Figures 4A-1 to 4C, Figures 5A-1 to 5B, or Figures 6A-1 to 6C-2, could be used in an antisense approach to inhibit translation of endogenous thymotaxin, Tango-63d, Tango-63e, Tango-67, or huchordin mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon.

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